REMARKS

In the Office Action mailed August 4, 2006, the Examiner required a restriction between Group I (claims 1 – 9) and Group II (claims 10 – 18). Office Action at page 2. The Examiner stated that if the Applicant elected invention II, then they should select either one primer or one primer pair selected from the group consisting of SEQ ID No 3 – 10. *Id* at page 3. In a September 5, 2006 response, the Applicant elected invention II with traverse. Amendment at page 5. The Applicant requested reconsideration of the requirement, stating that the primers are designed "to operate as pairs, in order to achieve exponential amplification." *Id.* The Applicant reluctantly amended the independent claims to SEQ ID NO: 7, and stated they elect SEQ ID NO: 7. *Id* Independent claims 11 and 12 were further amended to remove a range of SEQ ID numbers and limit the claim to SEQ ID 5.

On November 1, 2006, the Examiner responded by stating that the Applicant did not elect a primer pair but instead elected a single nucleic acid. Office Action at page 2. As such, the Examiner did not examine claims with primer pairs. *Id.* Further, the Examiner did not find the arguments persuasive because each of the claims do not require the use of a second primer, and claims 10 and 19 only require one primer. *Id* at page 2 – 3.

The Applicant thanks Examiner Myers for her time on March 27, 2007 to clarify the Examiner's statements. It is our understanding that once the independent claims are allowed, if the dependent claim comprises an additional primer, we may rejoin the claims. As such, when allowable claims are indicated, any non-examined or superfluous claims will be cancelled.

I. 35 U.S.C. § 112 REJECTIONS

The Examiner has rejected claims 10, 18, 19, 20 and 22 under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner states that the language is indefinite for failing to recite a clear nexus between the preamble of the claims and the final process step of the claims. Office Action at page 4. The Applicant amended the claims to clarify the claim language to state the method is for detecting an enterovirus and therefore respectfully requests the Examiner withdraw the rejection. In addition, the Examiner stated that the claims were indefinite over the recitation of "optionally" in the claims because it is unclear as to what is intended to be the relationship between SEQ ID NO.: 7 and the optional sequence. *Id.* The Applicant amended the

claim to remove the optional sequence. As such, the Applicant respectfully requests the Examiner withdraw the rejection. Further, the Examiner stated that the claims were indefinite over the recitation of "selected amplification reaction." *Id.* The Applicant has removed this language and therefore respectfully requests the Examiner withdraw the rejection.

The Examiner stated that the claims were indefinite over the recitation "the target binding sequence" because the phrase lacked proper antecedent basis. *Id.* The Applicant, per the Examiner's suggestion, amended the claims to recite "a target binding sequence." As such, the Applicant respectfully requests the Examiner withdraw the rejection. The Examiner also stated claim 18 was indefinite over the recitation "the oligonucleotide" because the phrase lacked antecedent basis. The Applicant amended the claim to recite "an oligonucleotide" and thus respectfully requests the Examiner withdraw the rejection. The Examiner also stated claim 20 and 22 were indefinite. Applicant believes the current claim amendments clarify the claims and respectfully requests the Examiner withdraw the rejection.

I. 35 U.S.C. § 103(A) REJECTIONS

Claims 10, 18, 19, 20 and 22 stand rejected under 35 U.S.C § 103(a) as being obvious over Yoon WO 03/014397 ("Yoon") in view of the Nycz article of Analytical Biochemistry, 259:226 – 34; 1998 ("Nycz") on the grounds set forth in pages 6 – 12 of the Official Action. This rejection is respectfully traversed.

The present invention is directed to methods of detecting the presence of an enterovirus target sequence in a sample. A method according to the principles of the present invention is set forth in amended claims 10, 18, 19, 20 and 22. In particular, the amended independent claims 10 and 19 requires mixing a sample that may contain an enterovirus target sequence with a first amplification primer having a sequence consisting essentially of the target binding sequence of SEQ ID NO:7; allowing the enterovirus target sequence to hybridize with said first amplification primer; amplifying the target sequence by use of said first amplification primer; and detecting the amplified target sequence, whereby detection of said amplified target sequence indicates said enterovirus target sequence is present in said sample.

The Examiner states that Yoon uses a 20 nucleotide primer that contains the 14 nucleotides of SEQ ID NO: 7. Office Action at page 7. *Id.* The Examiner further states that Nycz teaches methods of detecting a target RNA sequence comprising use of strand displacement amplification with a primer of three regions: a first 3' region that is complementary to an HIV target

binding sequence, a BsoBI restriction enzyme site 5' of the target binding sequence and which is the sequence CTCGGG, and a third 5' sequence that is not complementary to the target sequence and which consists of the sequence CGATTCCGCTCCAGACTT. *Id.* at page 7 – 8. As such, the Examiner alleges that it would have been obvious to one of ordinary skill in the art to modify "the method of Yoon so as to have amplified the enterovirus nucleic acids using the RT-SDA method of Nycz..." *Id.* at page 8. The Applicant respectfully disagrees.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Evidence of unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) (Evidence showing that the claimed herbicidal compound was more effective than the closest prior art compound in controlling quackgrass and yellow nutsedge weeds in corn and soybean crops was sufficient to overcome the rejection under 35 U.S.C. 103, even though the specification indicated the claimed compound was an average performer on crops other than corn and soybean.). See also *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (unexpected superior therapeutic activity of claimed compound against anaerobic bacteria was sufficient to rebut *prima facie* obviousness even though there was no evidence that the compound was effective against all bacteria).

One of the surprising and unexpected advantages of the Applicants' instant invention is that the primers have minimal cross-reactivity with rhinovirus. Rhinoviruses are members of Picornaviridae and as such the rhinoviruses are very closely related genetically to enteroviruses. Indeed, as stated in the specification, at the time of the cited prior art it was well documented that

primers designed to detect enterovirus cross reacted with various strains of rhinovirus. *See*, specification at page 31; *Kessler et al.*, J. Clin. Microbiol. 35: 976 – 77 (1997). As such, the primers of the instant invention are superior in property to the enterovirus primers of the prior art.

Further, the Examiner alleges that it would have been obvious to one of ordinary skill in the art to modify "the method of Yoon so as to have amplified the enterovirus nucleic acids using the RT-SDA method of Nycz..." *Id.* at page 8. The Examiner further alleges that such a modification of Yoon would result in "modifying the EV2 primer of Yoon so that the primer was suitable for the RT-SDA reaction." *Id.* at pages 8 – 9. Moreover, the Examiner further alleges that modification of the Yoon primer by deleting 6 nucleotides would have been obvious to one of ordinary skill in the art. *Id.* at pages 9 – 10. The Applicant respectfully disagrees. First, neither reference suggests or motivates one to modify the EV2 primer of Yoon to be applicable to RT-SDA. More importantly, there is no reasonable expectation of success even if the primer were modified. The target binding region of the primer of the instant invention, SEQ ID NO: 7, is 14 nucleotides long. The target binding region of the primer of Yoon, EV2, is 20 nucleotides. To obtain the target binding region of SEQ ID No: 7, one would have to *add approximately 42% more nucleotides* to the target binding region of SEQ ID No: 7 to obtain the sequence of Yoon. Neither cited reference teaches or suggests such a gross modification to the target binding region. Moreover, simply adding or subtracting nucleotides does not give a reasonable expectation that there will be no cross-reactivity with rhinovirus.

In addition, the Examiner also states that "in the absence of evidence to the contrary" modification of the 5' non-target binding sequence of Nycz to obtain the non-coding sequence of the instant invention would have been obvious to one of ordinary skill in the art. *Id.* at page 8 – 9. The Applicant could find no suggestion or motivation in the cited references to modify the non-target binding region of the primer. Applicant respectfully requests the Examiner show where such suggestion or motivation lies. The Office Action lacks this necessary and critical elements. Further, it appears to the Applicant that the Examiner is taking an Official Notice of Facts without setting forth the Official Notice in the record. For example, Examiner seems to suggest that it would have been obvious to modify the non-target binding sequence of a primer used in reverse transcriptase - strand displacement amplification. The Applicant requests the Examiner state on the record if she is taking Official Notice of Facts and permit Applicant an opportunity to challenge these unsupported assertion if the Examiner is actually taking Official Notice. If no Official Notice is intended, Examiner is requested to clarify this issue.

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Furthermore, the Examiner stated that the phrase "consisting essentially of" means that additional nucleotides may be present at the 3' end or 5' end of the primer because the phrase was not clearly defined in the specification and there is "no art recognized definition for this phrase as it applies to nucleic acids." *Id.* at page 10. The Applicant is somewhat confused by this explanation and requests clarification. The MPEP clearly states that the phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original)." M.P.E.P. 2111.03. As stated previously, it is well known in the art that rhinoviruses are very closely related genetically to enteroviruses. Indeed, as stated in the specification, at the time of the cited prior art it was well documented that primers designed to detect enterovirus cross reacted with various strains of rhinovirus. *See*, specification at page 31; *Kessler et al.*, J. Clin. Microbiol. 35: 976 – 77 (1997). As such modification of a primer could materially affect the basic and novel characteristic of the primer, resulting in cross reactivity with other viruses. The specification clearly indicates that the primers of the instant invention are novel as they do not cross react with rhinovirus. *See*, page 31 of specification. Indeed, to demonstrate that the enterovirus does not cross react with rhinovirus, the Applicant performed the experiments of Example 5. *Id.* Further, it has been recognized by the courts that the language "consisting essentially of" for nucleotide sequences can be construed to exclude from the nucleotide sequence the presence of additional sequences. *See, Regents of Univ of Cal. v Eli Lilly & Co*, 119 F.3d 1559, 1573 (Fed. Cir. 1997); *writ of certiorari denied* 523 U.S. 1089 (U.S. 1998).

For the reasons state above, Applicant respectfully requests that the Examiner withdraw the rejections of independent claim 10 and 19. Finally, as claims 18, 20 and 22 are dependent upon claims 10 and 19, which we believe are allowable, we request that the Examiner withdraw the rejections.

CONCLUSIONS

Based on the foregoing, further and favorable action in the form of a Notice of Allowance is earnestly solicited. Should the Examiner feel that any issues remain, it is requested that the attorney for Applicants listed below be contacted so that any such issues may be adequately addressed and prosecution of the instance application expedited.

A Credit Card Payment Form is attached for payment of the extension fees. Applicants believe no other fees are due with this response. If, however, additional fees are due, please charge our Deposit Account No. 50-2228, under Order No. 020187.0187PTUS from which the undersigned is authorized to draw.

Dated: April 2, 2007

Respectfully submitted,

By _____

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